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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/752,639	12/29/2000	Tetsuya Gatanaga	IRVN-007CON2	1505

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EXAMINER	
MURPHY, JOSEPH F	
ART UNIT	PAPER NUMBER
1646	10

DATE MAILED: 09/26/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/752,639	GATANAGA ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-58* is/are pending in the application.

4a) Of the above claim(s) *34,41-44,46-50 and 52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33, 35-40, 45, 51, 53-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Formal Matters

Claims 33-34 were amended, and new claims 35-58 were added in Paper No. 8, 6/24/2002.

Election/Restrictions

Applicant's election with traverse of Group IX, claims 33-34 as drawn to a method of screening a substance for an ability to affect TRRE activity, wherein the polypeptide has the sequence of SEQ ID NO: 9, in Paper No. 8, 6/24/2002 is acknowledged. The traversal is on the ground(s) that there would be no burden to search methods using the other polypeptides. This is not found persuasive for the following reasons. Applicant's attention is directed to MPEP 808.02 which states that "Where the related inventions as claimed are shown to be distinct under the criteria of MPEP 806.05 (c-i), the examiner, in order to establish reasons for insisting upon restriction, must show by appropriate explanation one of the following: (A) Separate classification thereof; (B) A separate status in the art when they are classifiable together; (C) A different field of search." As set forth in the Restriction requirement, Groups I-XVI are independent and distinct, each from the other, because they are products which possess characteristic differences in structure and function, and each has an independent utility, that is distinct for each invention which cannot be exchanged. Applicant argues that no burden is placed on the examiner to consider all claims. As discussed in (b), the separate status in the art as set forth in the Restriction requirement demonstrates that each distinct Group requires a separate field of search, and a search of one Group would not reveal art on the other Groups, thus imposing a burden on the examiner.

The requirement is still deemed proper and is therefore made FINAL. Claims - read on the elected Group and are under consideration. Claims 34, 41-44, 46-50, 52 are withdrawn from consideration pursuant to 37 CFR 1.142(b).

Specification

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Objections

Claims 35, 39 and 40 are objected to because of the following informalities: They contain limitations drawn to non-elected inventions. Appropriate correction is required.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35, 39, 40, 45, 51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening substances for an ability to affect the TRRE activity of the protein encoded by SEQ ID NO: 9, does not reasonably provide enablement for a method of screening substances for an ability to affect the TRRE activity of the protein encoded by a fragment of the longest open reading frame of SEQ ID NO: 9, or a method of screening substances for an ability to affect the TRRE activity of the protein encoded by a polynucleotide that hybridizes to a nucleic acid that encodes SEQ ID NO: 9. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 35, 39, 40, 45, 51 are overly broad since no guidance is provided as to which of the myriad of polypeptide species encompassed by the claim will retain the characteristics the polypeptide encoded by SEQ ID NO: 9. Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible muteins of TRRE. It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. For example, Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph).

Since the claims encompass methods using muteins of TRRE, and given the art recognized unpredictability of the effect of mutations on protein function, it would require undue experimentation to practice the claimed method. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors considered to be relevant in the instant case are set forth below:

(1) the breadth of the claims - The claims are drawn to a method of screening substances for an ability to affect the TRRE activity of the protein encoded by a fragment of the longest open reading frame of SEQ ID NO: 9, or a method of screening substances for an ability to affect

the TRRE activity of the protein encoded by a polynucleotide that hybridizes to a nucleic acid that encodes SEQ ID NO: 9.

(2) the nature of the invention - The instant invention is a method of compound identification.

(3) the state of the prior art - The Voet reference demonstrates that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function.

(5) the level of predictability in the art - The Voet reference demonstrates the unpredictability of the protein art.

(6) the amount of direction provided by the inventor - Applicant has only taught methods using TRRE, with the amino acid sequence as encoded by SEQ ID NO: 9, not mutants of TRRE.

(7) the existence of working examples - Working examples are provided only for one TRRE, not mutants of TRRE.

(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. Given the breadth of claims 35, 39, 40, 45, 51 in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to practice the claimed invention.

Claims 35, 39, 40, 45, 51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed,

had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

These are genus claims. According to the specification, the term variant means a protein having one or more amino acid substitutions, deletions, insertions and/or additions made to the polypeptide encoded by SEQ ID NO: 9. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to the polypeptide encoded by SEQ ID NO: 9. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Although the specification states that these types of changes are routinely done in the art, the specification and claim do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the polypeptide encoded by SEQ ID NO: 9 alone is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 33, 35-40, 45, 51, 53-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 35, 40 and 51 recite the term "stringent conditions", which is a conditional term and renders the claim indefinite. Furthermore, some nucleic acids that might hybridize under conditions of moderate stringency, for example, would fail to hybridize under conditions of high stringency. The metes and bounds of the claim thus cannot be ascertained. This rejection could be obviated by supplying specific conditions supported by the specification that Applicant considers to be "stringent". Claims 39, 45, 51 are rejected insofar as they depend on the recitation in claim 35 of "stringent conditions".

Claim 33 is vague and indefinite in the recitation of the terms "TRRE". There is no definition within the claim to define the protein to which this acronym refers. Thus, the metes and bounds of this claim cannot be determined. Claims 35-40, 45, 51, 53-58 are rejected insofar as they depend on the recitation in claim 1 of "TRRE".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 33, 37-38, 53-56, 58 are rejected under 35 U.S.C. 102(b) as being anticipated by Katsura et al. (1996).

Katsura et al. teaches a method of testing substances for their effects on the release of soluble TNF receptor from tumor cells expressing TNF receptor. This method comprises a cell expressing TNF receptor, a substance to be tested, and a polypeptide that causes TNF receptor to be cleaved, and measurement of the soluble TNF receptor released (Katsura et al. at 299, 301). Thus claim 33 is anticipated. Katsura et al. teaches the transfection of a cell with cDNA encoding TRRE for use in the method (Katsura at 299), thus claim 37 is anticipated. Katsura et al. teaches that TRRE is a metalloprotease (Katsura at 301), thus claim 38 is anticipated. Katsura et al teaches that cell lines expressing both p55 and p75 TNF receptor were used (Katsura et al. see abstract, the THP-1 cells express both p55 and p75 TNF receptor), thus claims 53-56 are anticipated. The TNF receptor released as a result of TRRE activity was measured in culture medium (Katsura at 299), thus claim 58 is anticipated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 33, 37-38, 53-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Katsura et al. (1996) in view of Bjornberg et al. (1995).

Katsura et al. teaches a method of testing substances for their effects on the release of soluble TNF receptor from tumor cells expressing TNF receptor. This method comprises a cell expressing TNF receptor, a substance to be tested, and a polypeptide that causes TNF receptor to be cleaved, and measurement of the soluble TNF receptor released (Katsura et al. at 299, 301). Katsura et al. teaches the transfection of a cell with cDNA encoding TRRE for use in the method (Katsura at 299). Katsura et al. teaches that TRRE is a metalloprotease (Katsura at 301). Katsura et al teaches that cell lines expressing both p55 and p75 TNF receptor were used

(Katsura et al. see abstract, the THP-1 cells express both p55 and p75 TNF receptor). The TNF receptor released as a result of TRRE activity was measured in culture medium (Katsura at 299).

Katsura et al. does not teach a method of testing substances for their effects on the release of soluble TNF receptor from tumor cells expressing TNF receptor wherein the binding of TNF to the surface of the cell is the indicator of TRRE activity. Bjornberg et al. teaches methods of measuring the proteolytic processing of the two TNF receptors (TNF-R55 and TNF-R75) into soluble forms in the myeloid cell lines U-937 and THP-1 (Bjornberg at 419, Table 1). Phorbol myristate acetate (PMA) rapidly stimulated release of soluble forms of both TNF-receptors. Bjornberg further teaches that 1,10-phenanthroline also reduced PMA-induced down-regulation of TNF-receptors in both cell lines as judged by TNF-binding to cells (Bjornberg at 421, Figure 2). Thus, it would have been obvious to one of skill in the art at the time the invention was made to practice a method of testing substances for their effects on the release of soluble TNF receptor from tumor cells expressing TNF receptor wherein the binding of TNF to the surface of the cell is the indicator of TRRE activity. The motivation is provided in Bjornberg et al. who teaches that PMA-induced down-regulation of TNF-binding in myeloid cells depends on metalloproteases and identification of pharmacological drugs to modulate this effect would be valuable (Bjornberg at 423).

Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Identification and characterization of soluble TNF receptor releasing enzyme (TRRE) from PMA-stimulated human monocytic THP-1 cells. Katsura, K. ; Park, M. ; Gatanaga, M.; Takishima, K.; Granger, G. A.; Gatanaga, T. Proceedings of the American Association for Cancer Research Annual Meeting, (1996) Vol. 37, No. 0, pp. 492. Meeting Info.: 87th Annual Meeting of the American Association for Cancer Research Washington, D.C., USA April 20-24, 1996..

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245. The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
September 19, 2002